Claims:

1. A method of producing a composition comprising a protein antigen, said method comprising the steps of:

a) providing a plurality of samples comprising a protein, said samples differing with respect to the conformation state of said protein;

b) identifying a sample from said plurality of samples that comprises a conformational variant of said protein capable of stimulating the production of neutralizing antibodies, against a pathogen from which said protein was derived.

2. The method of claim 1, wherein said conformational variants have the same primary amino acid sequence, but differ with respect to their secondary or tertiary structure.

3. The method of claim 1, wherein said method comprises the step of clustering samples based on a profile of selected criteria.

4. The method of claim 3, wherein said criteria comprises the ability to bind or the affinity for an antibody, or antigen binding fragment thereof, or plurality of antibodies specific for said protein.

5. The method of claim 4, wherein said antibody is:

a) a non-neutralizing antibody;

b) a neutralizing antibody;

c) a polyclonal antibody;

d) a monoclonal antibody;

e) contacted with said protein in the presence of biological fluids.

6. The method of claim 1, wherein:

a) said conformational variants are obtained by treating said protein in a native conformation under different conditions;

b) said conformational variants are obtained by treating a sample of protein having a native conformation under different conditions;

c) said conformational variants are obtained by treating a sample of denatured or partially denatured protein under different conditions; or

d) a secondary or tertiary structure of said conformational variant is stabilized.

7. The method of claim 1, wherein said identifying comprises identifying a sample comprising a protein conformational variant that:

a) binds to a neutralizing antibody;

b) binds to one or more neutralizing antibodies with a higher relative binding affinity than one or more non-neutralizing antibodies;

c) partially clears or clears neutralizing activity in serum *in vitro*;

d) stimulates the production of neutralizing antibodies *in vivo*;

e) binds a neutralizing antibody with a higher than the neutralizing antibody binds the native conformation;

f) wherein the affinity of a neutralizing antibody for the conformational variant is greater than the affinity of the neutralizing antibody for the native conformation;

g) wherein the increase in affinity of f) is greater than an increase in affinity of a non-neutralizing antibody for the conformational variant over the native conformation;

h) wherein the affinity of a neutralizing antibody for the conformational variant is greater than the affinity of the neutralizing antibody for a native conformation, but wherein there is no difference or a decrease in affinity of a non-neutralizing antibody for the conformational variant over the native conformation.

8. The method of claim 1, wherein said protein is structurally characterized using method selected from the group consisting of:

circular dichroism spectropolarimetry, fluorescence spectroscopy using either intrinsic or extrinsic fluorescent probes, mass spectroscopy, UV-VIS spectroscopy, NMR, small angle X-ray scattering, enzymatic activity, ion exchange, hydrophobic interaction, reverse phase chromatography, gel filtration and affinity.

9. The method of claim 6, wherein said conformational variant is stabilized using a covalent linker.

10. The method of claim 9, wherein covalent linker targets an amino group, a carboxyl group, a hydroxyl group, a carbohydrate or a glutaraldehyde.

11. The method of claim 9, wherein said linker target is created by *in vitro* mutagenesis of the amino acid sequence or a nucleic acid sequence encoding said protein.

12. The method of claim1, wherein a purification step enriches a sample for a conformational variant.

13. The method of claim 12, wherein said sample is enriched for a conformational variant using ion exchange, chromatography, hydrophobic interaction chromatography, reverse phase chromatography, gel filtration chromatography or affinity chromatography.

14. The method of claim 12, wherein said samples are enriched using one or more neutralizing antibodies.

15. The method of claim 4, wherein said affinity is measured using a method selected from the group consisting of: ELISA, surface plasma resonance, gel mobility shift assay, isothermal titration calorimetry equilibrium dialysis, centrifugation and fluorescent resonant energy transfer.

16. A method according to claim 1, which further comprises contacting each conformational variant sample with a non-neutralizing and a neutralizing antibody and identifying a sample comprising a conformational variant or subset that binds to the neutralizing antibody with higher affinity than to the non-neutralizing antibody.

17. A method according to claim 1, wherein said conformational variant is bound to a microparticle having a diameter up to 150 μm.

18. A method according to claim 17, wherein said microparticle comprises biodegradable polymer or other biodegradable microparticle material.

19. A method according to claim 17, wherein:

(a) said microparticle comprises said conformational variant bound to its outer surface;

(b) the microparticle core is surrounded by a pharmaceutically acceptable coating agent, that is releasable *in vivo*;

(c) said coating agent of (b) is selected from the group consisting of a biodegradable polymer, calcium phosphate, cellobiose and polyethylene glycol;

(d) said biodegradable polymer of (c) is selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), poly (D,L-lactide-polyethylene glycol), a poly(sulphobutyl-polyvinylalcohol)-g-(lactide-co-glycolide), a polyhydroxybutyric acid, a polycaprolactone, a polyothoester, a polyanhydride, a polyesteramide, a polyamino acid, a polycyanoacrylate, a polyamide, a polyacetal, a polyetherester, a polydioxanone, a polyalkene alkylate and a biodegradable polyurethane;

(e) the microparticle comprises a pharmaceutically acceptable biodegradable polymer;

(f) said biodegradable polymer of (e) is selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), poly (D,L-lactide-polyethylene glycol), a poly(sulphobutyl-polyvinylalcohol)-g-(lactide-co-glycolide), a polyhydroxybutyric acid, a polycaprolactone, a polyothoester, a polyanhydride, a polyesteramide, a polyamino acid, a polycyanoacrylate, a polyamide, a polyacetal, a polyetherester, a polydioxanone, a polyalkene alkylate and a biodegradable polyurethane;

(g) the microparticle comprises a metal salt;

(h) said metal salt of (g) is calcium hydroxide or aluminium hydroxide;

(i) the method further comprises a step of covalently linking the protein antigen to the surface of the microparticle;

(j) said microparticle further comprises an immunostimulatory molecule;

(k) wherein said immunostimulatory molecule of (j) is a molecule that results in an elevated humoral response;

(l) wherein said immunostimulatory molecule of (k) is IL-4, IL-5, IL-6, IL-10 and IL-13.

20. A pharmaceutical composition comprising a conformational variant obtained by the method of claim 1.

21. A pharmaceutical composition according to claim 20, wherein the conformational variant is a protein antigen that binds to a neutralizing antibody with a higher affinity than a non-neutralizing antibody.

22. A pharmaceutical composition according to claim 20, wherein the structure of the conformational variants is stabilized.

23. A pharmaceutical composition according to claim 1, wherein the conformational variant protein antigen is capable of partially clearing or clearing neutralizing activity in serum *in vitro*.

24. The pharmaceutical composition of claim 20, further comprising a microparticle.

25. A pharmaceutical composition according to claim 24, wherein:

(a) said microparticle comprises a core comprising at least one protein molecule that comprises the same primary amino acid sequence as the protein antigen;

(b) said microparticle comprises a protein core composed of at least one protein molecule having greater than 95% amino acid sequence identity as the protein antigen;

(c) the protein core of (a) is surrounded by a pharmaceutically acceptable coating agent, that is releasable *in vivo*;

(d) said coating agent of (c) is selected from the group consisting of a biodegradable polymer, calcium phosphate, cellobiose and polyethylene glycol;

(e) said biodegradable polymer of (d) is selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), poly (D,L-lactide-polyethylene glycol), a poly(sulphobutyl-polyvinylalcohol)-g-(lactide-co-glycolide), a polyhydroxybutyric acid, a polycaprolactone, a polyothoester, a polyanhydride, a polyesteramide, a polyamino acid,

a polycyanoacrylate, a polyamide, a polyacetal, a polyetherester, a polydioxanone, a polyalkene alkylate and a biodegradable polyurethane;

(f) the microparticle comprises a pharmaceutically acceptable biodegradable polymer;

(g) said biodegradable polymer of (f) is selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), poly (D,L-lactide-polyethylene glycol), a poly(sulphobutyl-polyvinylalcohol)-g-(lactide-co-glycolide), a polyhydroxybutyric acid, a polycaprolactone, a polyothoester, a polyanhydride, a polyesteramide, a polyamino acid, a polycyanoacrylate, a polyamide, a polyacetal, a polyetherester, a polydioxanone, a polyalkene alkylate and a biodegradable polyurethane;

(h) the microparticle comprises a metal salt;

(i) said metal salt of (h) is calcium hydroxide or aluminium hydroxide;

(j) the protein antigen is covalently bound to the surface of the microparticle.

26. A pharmaceutical composition according to claim 20, wherein said composition further comprises an immunostimulatory molecule.

27. A pharmaceutical composition according to claim 26, wherein said immunostimulatory molecule is a molecule that results in an elevated humoral response.

28. A pharmaceutical composition according to claim 27, wherein said immunostimulatory molecule is IL-4, IL-5, IL-10 and IL-13.

29. A pharmaceutical composition according to claim 20:

a) suitable for causing an immune response in for immunization of a subject against a pathogen;

b) which further comprises a second protein antigen;

c) which further comprises an adjuvant; or

d) suitable for partially or fully immunizing a subject against a pathogen from which the conformational variant was derived.

30. The pharmaceutical composition of claim 29, wherein said pathogen is a:

a) virus;

b) bacteria; or

c) fungus.